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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 031/725, 031/685, 009/127

A1

(11) International Publication Number: **WO 91/12026**

(43) International Publication Date: 22 August 1991 (22.08.91)

(21) International Application Number: PCT/AU91/00052

(22) International Filing Date: 14 February 1991 (14.02.91)

(30) Priority data:
PJ 8629 14 February 1990 (14.02.90) AU

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: MEANS OF REDUCING SURGICAL ADHESIONS

(57) Abstract

A method of reducing surgical adhesions in a patient by means of coating the tissue surfaces with a phospholypid, preferably lecithin, in suspension or solution in an inert carrier, such as for example, water, saline, or propylene glycol, or mixtures thereof. Hyaluronic acid, or its salts, may also be present in the mixture.

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MEANS OF REDUCING SURGICAL ADHESIONS

TECHNICAL FIELD

The present invention relates to a method for reducing or preventing unwanted adhesions between tissue surfaces in both humans and animals after surgery or other trauma.

BACKGROUND ART

Most surgery involves an incision in the skin followed by further incisions into deeper tissue as needed. Upon completion, the two edges of each incision are held together by sutures or other means, to promote healing by enabling the cells at the open ends to proliferate and fuse together. A problem arises when tissue union not only occurs between the edges produced by this incision, but also between these edges and those of adjacent incisions. These fibrous unions can become vascularized to form tissue "bridges", which represent tight binding between two tissue surfaces which would otherwise slide over each other as easily as they did before surgery. These tissue "bridges" are known as "surgical adhesions". They are most undesirable where they inhibit the relative movement of adjacent tissue surfaces and are often manifest as stiffness, or immobility. If motion is forced, surgical adhesions can result in pain or they may rupture to produce haemorrhage.

Repeat surgery seldom cures the problem because surgical adhesions usually reform in the same sites. Individuals vary greatly in their susceptibility and some tissues are more prone than others. Surgical adhesions are common in abdominal surgery but can occur unpredictably in almost any surgical procedure. Although deaths from abdominal surgery are rare, the major cause is surgical adhesions.

Adhesions can also occur without surgery. However, it is not known what causes them to form and what prevents them forming between adjacent tissue surfaces under normal physiological conditions.

Among previous methods known to prevent surgical adhesions is the use of hyaluronic acid, which has resulted in modest improvements, or else by interposing a barrier along the fascial plane between the incisions, which is later removed by a subsequent incision in the skin. Alternatively, a barrier material which is eventually digested without an inflammatory reaction has been used. However, the barrier method has been found to be limited in its application.

It is an object of the present invention to provide an improved method of reducing surgical adhesions which will substantially overcome, or ameliorate, the abovementioned disadvantages. The present invention is therefore directed to a means of preventing surgical adhesions which is simple, safe, inexpensive and easy to apply.

DISCLOSURE OF THE INVENTION

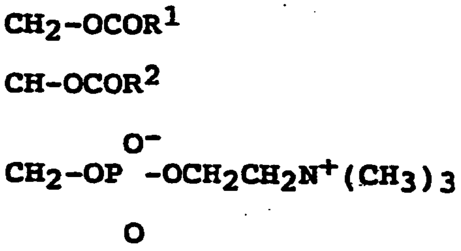
This invention is based upon the principle that the tissue "bridges" constituting surgical adhesions will not form if there is no physical adhesion between adjacent surfaces. If they form between surfaces that never move relative to each other, then their formation is unlikely to be manifest clinically. The task is therefore one of preventing the sticking of adjacent surfaces which normally slide over each other easily, since the formation of tissue "bridges" restricts movement, or causes pain or haemorrhaging.

It is desirable that any barrier should have one or more of the following functions. It should act as a release agent to prevent sticking. It should act as a lubricant facilitating sliding of adjacent surfaces. This needs to be a boundary lubricant since any fluid could be squeezed out under load leaving direct solid-to-solid contact of the two tissue surfaces. It should provide a biological barrier.

Phosphatidylcholine, commonly known as lecithin, is a phosphatide found in all living organisms (plants and animals). It is a constituent of biological membranes and is involved in permeability, oxidative phosphorylation, phagocytosis, and chemical and electrical excitation.

Phosphatidylcholine has been identified in many animal tissues and organs such as the brain, nervous system, liver, heart, lungs, kidneys, blood, milk, sperm, in micro-organisms and throughout the vegetable kingdom.

Lecithin is a mixture of the diglycerides of stearic, palmitic and oloeic acids linked to the choline ester of phosphoric acid and can be represented by the general formula I



$$\begin{array}{l} CH_2\text{-}OCOR^1 \\ CH\text{-}OCOR^2 \\ CH_2\text{-}O\overset{O^-}{\underset{O}{P}}\text{-}OCH_2CH_2N^+(CH_3)_3 \end{array}$$

(I)

wherein R1 and R2 are fatty acid residues. Usually one acid is saturated and the other unsaturated.

Phosphatidylcholines are highly surface active as witnessed by "surfactants" in the lung. International Patent Application PCT/AU88/00322 discloses the ability of phosphatidylcholines to form sheets of molecules in parallel planes which can slide over each other providing very low coefficients of kinetic friction in the range 0.002-0.006 or lower. Moreover it could provide these values under a high load of up to 18 Kg/cm^2. The same phospholipid was also a good release agent, reducing the force of adhesion by at least 99%.

However it is completely unexpected that phospholypids act to prevent or reduce the occurrence of surgical adhesions. The discovery that phospholipid applied to a traumatised tissue surface will ameliorate the formation of surgical adhesion has led to the present invention.

The present invention therefore concerns a method for the reduction or prevention of unwanted surgical adhesion between two tissue surfaces in an animal including a human, which comprises interposing between said surfaces an effective amount of a phospholipid suspension or solution comprising a phospholipid and a sterile surgically acceptable carrier.

Suitable phospholipids for use in the present invention are listed in Table 1, although other phospholipids can also be used. Mixtures or combinations of the phospholipids are also permissible.

Table 1
PHOSPHOLIPIDS

Phosphoglycerides

phosphatidic acids
cytidylic phosphoglycerides (CDP diglyceride)
choline phosphoglycerides
ethanolamine phosphoglycerides
N-methylethanolamine phosphoglyceridesN,N-dimethylethanolamine phosphoglycerides
N-acylethanolamine phosphoglyceride
serine phosphoglycerides
N-2-(hydroxyethyl)alanine phosphoglyceride
glycerol phosphoglycerides
glycerophosphate phosphoglycerides
phosphatidylglycerol phosphoglyceride (diphosphatidylglycerol)
mono and diacylglycerol phosphoglycerides (lysobisphosphatidic acids)
glucosaminylglycerol phosphoglyceride
O-amino acid esters of glycerol phosphoglycerides
inositol phosphoglyceride
inositol monophosphate phosphoglyceride
inositol diphosphate phosphoglyceride
monomannosyl-hexamannosyl inositol phosphoglycerides
glucose phosphoglyceride
O-diglucosylglycerol phosphoglyceride

Phosphoglycolipids

diacyl (glycerylphosphoryldiglucosyl) glycerol

Phosphodiol lipids

acyl dihydroxyacetone phosphate
alkyl dihydroxyacetone phosphate

Phosphosphingolipids

sphingomyelin (ceramide phosphorylcholine)
ceramide phosphorylethanolamine
ceramide phosphorylglycerol
ceramide phosphorylglycerophosphate
ceramide phosphorylinositol-containing lipids

Preferably the phospholipid is phosphatidylcholine (lecithin). Further, other phospholipids such as phosphatidylethanolamines, phosphatidylinositols, phosphatidylserines, phosphatidylglycerides and sphingomyelin may also be used in admixture with the phosphatidylcholine.

Phospholipids can be used alone, or together with other substances such as hyaluronic acid. Such mixtures have an advantage of an improved ability to stay in suspension. Further, there are advantages and synergism between the phospholipids and hyaluronic acid, in the performance of the invention, in some situations.

In addition, the phospolypid can be combined with or dissolved in substances such as propylene glycol and related substances, provided they are non-toxic and suitable for application to organ and skin surfaces in surgery.

The poor solubility of phospholipid, and especially DPPC and other phosphatidylcholines, may also be overcome by dispersing them using ultrasound, preferably in an aqueous solution of sodium hyaluronate, or in saline solution, for example.

The purity of the phospholipid is normally 99%, however less pure phospholipid may also be used, since certain impurities may act synergistically, e.g. in phosphatidylcholine the impurities tend to be phosphatidylethanolamines, phosphatidylinostols, phosphatidylserines, phosphatidylglycerides and sphingomyelin.

However, it is highly desirable to exclude certain impurities such as lysophosphatidylcholines. The levels of these impurities should preferably be kept below 0.1%.

The phospholipid suspension of the invention may comprise a phospholipid dispersed in a neutralized solution of hyaluronic acid. The concentration of the phospholipid suspension is preferably about 3 mg ml^{-1} of phospholipid disbursed in 10 mg ml^{-1} of a neutralized solution of hyaluronic acid. The phospholipid may also be dispersed in a solution of sodium hyaluronate. The phospholipid can be dispersed by any suitable means, such as by ultrasound.

Alternatively, the phospholipid may be dissolved in propylene glycol, (or similar non-toxic substances) and optionally further diluted with water. If desired hyaluronic acid of a salt of hyaluronic acid may also be included in this solution.

Preferably the phospholipid suspension or solution is in the form of a gel, paste or viscous solution to assist in its application to the tissue surfaces.

The phospholipid suspension or solution may be applied and then re-applied at regular intervals after the first application.

The phospholipid suspension is applied to the interface between the tissue surfaces of the surgical incision at the time of surgery, preferably with top-up doses administered by injection for up to 14 days afterwards.

Usually the suspension or solution should not be applied to the tissue surfaces that are to be rejoined, and which are sutured together.

The method of application may be by coating the surfaces by means of a brush, spray, or even manually. If the surgery permits, the organ or surface can be dipped in the solution or suspension of phospholipid. Any suitable method of application can be used.

MODES FOR CARRYING OUT THE INVENTION

The invention is now described with reference to some examples.

EXAMPLES

In the following Examples the prevention of absolute alcohol-induced caecal adhesions, mechanically induced caecal adhesions and talc-induced adhesions were demonstrated on Wistar rats.

The incidence of adhesions was scored on a scale of 0-4 as below.

0 - no adhesions present
1 - thin filmy, easily separated adhesions
2 - vascularized but separable adhesions
3 - moderate vascularized, adhesions
4 - grossly disseminated inseparable adhesions

EXAMPLE 1 - The prevention of absolute alcohol induced caecal adhesions in rats.

A left flank laparotomy was conducted on 33 adult female Wistar rats under halothane anaesthesia (4% induction, 1% maintenance).

The surgical site was clipped and disinfected using alcoholic iodine. The caecum was exteriorized in all rats.

In 10 rats, 1ml of saline was applied to each lateral surface and a further 1ml of saline was instilled into the peritoneal cavity upon return of the caecum.

In the remaining 23 rats, the caecum was swabbed with absolute alcohol on each lateral surface and then treated as above with either saline, Hyaluronic Acid or Hyaluronic Acid plus phospholipid.

The abdominal wall was closed with 4-0 Ethiflex (Ethicon) mattress sutures. The skin was then closed using subcuticular sutures (4-0 Ethiflex) and the wound treated with Neotracin and Nobecutane (Astra Pharmaceuticals).

Food intake was monitored for fourteen days to ensure adequate recovery. After fourteen days the animals were sacrificed by CO_2 inhalation and cervical dislocation.

RESULTS

Treatment	No. of rats	Adhesion scores
Saline	8	0 ± 0
alcohol	10	2.8 ± 0.39
alcohol + HA	6	3.7 ± 0.21*
alcohol + HA + PL	9	1.7 ± 0.33

*significantly different from the alcohol control ($P<0.05$).

The saline treated control rats showed no adhesions, whereas alcohol treated rats, showed substantial adhesions.

The addition of HA to the alcohol treated rats showed no significant effect on the incidence of adhesions.

However, the addition of both HA and phospholipid to the alcohol treated rats significantly reduced the formation of adhesion by 39% ($P<0.025$).

EXAMPLE 2 - The prevention of mechanically induced caecal adhesions.

A left flank laparotomy was conducted on 19 adult male Wistar rats as described in Example 1.

However, instead of swabbing the caecum with alcohol, it was abrasively swabbed with a dry surgical swab until noticeable hyperaemia was present. They were then treated with either saline or HA and phospholipid as in Example 1.

After 14 days the rats were sacrificed.

RESULTS

Treatment	No. of rats	Adhesion scores
Saline	10	1.5 ± 0.27
HA + PL	9	0.56 ± 0.18*

*significantly different from saline control ($P<0.01$)

The rats treated with phospholipid and HA showed a significant decrease in the formation of adhesion by 63% ($P<0.025$).

EXAMPLE 3 - The prevention of talc induced adhesions.

Twenty adult male Wistar rats were injected intraperitoneally using an 18 gauge needle with 0.05ml/kg of a suspension of talc in saline (mg/ml w/v). The rats were split into two groups of 10. One group received a second ip injection of 0.5 mls/kg saline while the other received a second ip injection of 0.5mls/kg of phospholipid and HA.

After 14 days the rats were sacrificed by cervical dislocation.

RESULTS	Treatment	No. of rats	Adhesion scores
	Talc + Saline	5	3.4 ± 0.24
	Talc + PL	5	2.6 ± 0.4

The addition of talc to the rats caused substantial formation of adhesions.

The addition of phospholipid to the rats significantly reduced the formation of adhesion by 24%. However, when the rats received an additional injection of saline or phospholipid and HA, no significant effect on the incidence on these adhesions was noted.

INDUSTRIAL APPLICABILITY

The invention is intended for use in surgery as a method of preventing or reducing surgical adhesions in subjects.

The foregoing describes only some of the embodiments of the present invention and modifications, obvious to those skilled in the art, can be made thereto without departing from the scope of the present invention.

THE CLAIMS

1. A method for the reduction or prevention of unwanted surgical adhesions between two tissue surfaces in an animal, including a human, having undergone surgery or similar trauma, which comprises interposing between said surfaces an effective amount of a phospholipid in suspension or solution in a surgically acceptable carrier.

2. The method of claim 1 wherein the suspension or solution also includes hyaluronic acid or a surgically acceptable salt thereof.

3. The method of claim 1 wherein the carrier is water and/or propylene glycol.

4. The method claim 1 wherein the phospholipid is 99% pure phosphatidylcholine.

5. The method of claim 1 wherein the solution or suspension is in the form of a gel, paste or viscous solution.

6. A viscous solution of a phospholipid, propylene glycol and water for use to prevent or reduce surgical adhesions in a patient having undergone trauma or surgery.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 91/00052

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.^{5} A61K 031/725, 031/685, 009/127

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	A61K 031/725, 031/685, 009/127

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

MARTINDALE PHARMACOPOEIA (edition 29) (Pharmaceutical Press)
REMINGTON'S PHARMACEUTICAL SCIENCES (Edition 17) (MACK)

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X,Y	AU,A, 23208/88 (890331) (MacNAUGHT PTY LTD) 11 May 1989 (11.05.89)	1, 2, 4, 5
Y	AU,B, 65709/86 (587299) (ETHICON, INC) 4 June 1987 (04.06.87)	1-20

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 15 May 1991 (15.05.91)	Date of Mailing of this International Search Report 22 May 1991 (22.05.91)
International Searching Authority Australian Patent Office	Signature of Authorized Officer L TRISTRAM

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [] Claim numbers ...., because they relate to subject matter not required to be searched by this Authority, namely:

2. [] Claim numbers ...., because they relate to parts of the international application that do comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [] Claim numbers ...., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1. [] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest
[] The additional search fees were accompanied by applicant's protest.
[] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No

Form PCT/ISA/210 (extra sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL APPLICATION NO. PCT/AU 91/00052

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
AU 65709/86	EP 225162 YU 2028/86 US 4877619	IN 166447 ZA 8608964	JP 62155223 US 4937254
AU 23208/88	CN 1033239	EP 387252	WO 8901777

END OF ANNEX